REMARKS

I. Priority

A cross-reference to prior-filed applications that provide the basis for a claim of priority of invention for the invention claimed in the above claims has been added to the first page of the specification as required by paragraph 1 on pages 2 and 3 of the office action. The cross-reference states that the applicants claim the benefit of priority of invention based on U.S. Provisional Patent Application, Ser. No.: 60/443,745, filed January 30, 2003, under 35 U.S.C. 119 (e), which, in turn, claims the benefit of priority of invention based on DE 102 59 004.4, filed December 16, 2002, in Germany under 35 U.S.C. 119. This claim of priority was properly included in the German language Declaration filed with the original application papers on December 12, 2003.

Since the filing receipt dated April 27, 2004 (Confirmation number 1882) acknowledges the claim of priority based on both the aforementioned U.S. Provisional Patent application and the DE application, the petition required under 37 C.F.R. 1.78 (a) and surcharge required under 37 C.F.R. 1.17 (t) are not required according to the last paragraph on page 3 of the Office Action.

II. Formal Rejections

New claims 7 to 16 have been filed and the original claims 1 to 6 have been canceled. Original claims 1 to 6 were English translations of claims for a

foreign patent document, which were not drafted considering U.S. Patent Office Rules and U.S. Patent Laws.

Cancellation of claims 1 and 4 to 6 obviates their rejections under 35 U.S.C. 101 (page 4, office action) and 35 U.S.C. 112, paragraph for indefiniteness (page 7, office action). No "use" claims have been included in the new claims 7 to 16 since U.S. Patent Law does not permit that type of claim. However method-of-treatment claims 11 to 13 and pharmaceutical-composition claims 14 to 16 contain some of the subject matter of canceled claims 4 to 6. None of the new claims 7 to 16 include the subject matter of canceled claim 1.

Cancellation of claims 1 and 4 to 6 obviates their rejection under 35 U.S.C. 112, first paragraph, for lack of enablement. The new method of treatment claims 11 to 13 do not claim a method of preventing (prophylaxis) of the stated disorders/diseases. These claims only claim a method of treatment of the stated disorders/diseases, namely glucocorticoid-mediated hypogonadism, sexual dysfunctions, and/or infertility. However the Office Action admits in paragraph 6 on page 5 to 6 that the specification provides an enabling disclosure for therapy or treatment of the claimed disorders/diseases.

Cancellation of claims 1, 5 and 6 obviates the rejection under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement. Claim 1 was not limited to the compounds of formula I. Claims 5 and 6 depended on claim 1 and apparently were rejected on this ground for that reason.

The new claims 7 to 16 are limited to the compounds of formula (I) and page 5 of the Office Action admits that there is sufficient descriptive support in

the specification for the compounds of formula I and methods of treatment and pharmaceutical compositions limited to the compounds of formula I.

The new main compound claim 7 includes a somewhat different description of the allowable R_2 groups in order to avoid including indefinite wording. The original "groups", which were designated "sec. propyl alcohol" and "sec. propyl ether" (which are compound names, not group names), are now designated by their systematic chemical names "1-hydroxy-1-methylethyl group" and "1-methoxy-1-methylethyl" respectively. The basis for these systematic chemical names for allowable R_2 groups, the group at the 21 position in the steroid compound of formula I, is found in the formulae for exemplary steroid compounds # 15 and # 18 in the list of preferred steroid compounds in dependent claim 8.

The ethyl isocrotonate group that was added to the list of allowable R_2 groups is based on exemplary steroid compound # 10 in the list of preferred steroid compounds in dependent claim 8 and in the original claim 3.

The basis for the last paragraph in new main compound claim 7, which limits the substituent groups on the "substituted phenyl group", is found in the substituents of the phenyl group at the 21 position in the exemplary compounds recited in claim 8 and in the original claim 3. The exemplary compounds containing the substituted phenyl groups in claim 8 are steroid compounds # 2 to 7, 9, 11 to 14, 16, 17, and 19 to 21.

For the foregoing reasons it is respectfully submitted that new claims 7 to 16 should not be rejected under 35 U.S.C. 112, first paragraph, and/or 35 U.S.C.

112, second paragraph.

III. Anticipation Rejections

Claims 1, 5 and 6 were rejected under 35 U.S.C. 102 (b) as anticipated by Gebhard, et al (US 5,620,966).

Claims 1, 5 and 6 were rejected under 35 U.S.C. 102 (b) as anticipated by Groen, et al (US 6,072,068).

Claims 1, 5 and 6 were rejected under 35 U.S.C. 102 (b) as anticipated by Peeters (WO 95/04536).

These prior art references disclose steroid compounds, which are similar to some extent with the steroid compounds of formula (I) of the present application. However the original claim 1 was not limited to the compounds of formula I shown in claim 2, but instead claimed "use" of "glucocorticoid receptor antagonists" having certain binding affinities for the glucocorticoid receptor and the progesterone receptor. The prior art references did disclose glucocorticoid receptor antagonists.

However claims 1, 5, and 6 have been canceled, obviating the foregoing anticipation rejections because the new claims 7 to 16 are limited to the steroid compounds of formula I originally claimed in claim 2.

For the foregoing reasons it is respectfully submitted that none of the new claims 7 to 16 should be rejected under 35 U.S.C. 102 (b) as anticipated by Gebhard, et al (US 5,620,966); Groen, et al (US 6,072,068); or Peeters (WO 95/04536).

IV. Obviousness Rejections

A. Peeters Alone

Claims 1 to 6 were rejected as obvious under 35 U.S.C. 103 (a) over Peeters, et al (WO 95/04536).

Peeters does disclose antiglucocorticoid steroids substituted at both the 11β or 10β position having a general formula that encompasses the steroids of formula I of claim 7 above. However the steroids of formula I above are much more limited than the steroids of the general formula on page 2 of Peeters, et al.

The generic formula on page 2 of Peeters, et al, encompasses (according to a rough estimate) 30x20x20x6 the steroid compounds of formula I or about 100,000 times the number of compounds of formula I, because formula I has a comparatively limited number of substituents in comparison to the generic formula on page 2 of Peeters, et al.

Thus a case of *prima facie* obviousness cannot be based on the generic formula on page 2 of Peeters, et al, because the particular limited choice of substituent groups according to formula I in e.g. claim 7 is neither disclosed nor suggested by Peeters, et al. There is no motivation in Peeters, et al, to select the particular substituents in applicants' formula I based on the broad generic teaching on page 2 of Peeters, et al. See M.P.E.P. 2144.08 II. A. especially (4), "motivation and size of genus".

However Peeters, et al, does disclose similar exemplary compounds on page 4, lines 1 to 2, including the RU 38486, namely 11β-(4-dimethylamino)-

phenyl-17β-hydroxy-17α-propyn-1-yl-estra-4, 9-dien-3-one. However this compound differs from the compounds of formula I of applicants' claim 7 because the compounds of applicants' formula I have a methyl or alkoxy (R_1) substituted phenyl group at the 11 position, not a dimethylamino substituted phenyl group. At the 21 position the applicants' R_2 substituents are much larger and include more atoms (such as substituted phenyl or the t-butyl group) than lone methyl group (in propynyl) of RU 38486.

It is respectfully submitted that there are too many differences between the structures of applicants' steroid compounds of formula I and the steroid RU 38486. The steroid compounds of applicants' formula I cannot be considered to be structurally obvious from the latter prior art compound RU 38486. The disclosure of Peeters, et al, would not "put the applicants' compounds in the hands of the public".

Applicants' claim 7 is a claim for new compounds and should be treated as such. Applicants' claimed compounds are entirely different in their structure from Peeters, et al. They are not structurally obvious from this reference.

The analysis regarding the other preferred steroids of Peeters, et al, on page 4, lines 4 to 12, is similar to the analysis in the case of RU 38486. Four preferred steroids are listed between these lines. However this compound of Peeters differs from the compounds of formula I of applicants' claim 7 because the compounds of applicants' formula I have a methyl or alkoxy substituted phenyl group at the 11 position, not a dimethylamino substituted phenyl group, and at the 21 position the closest group of the applicants to the group of Peeters

is the aminoacetate substituted phenyl group, which is different from the dimethylamino substituted phenyl group of the Peeters reference. The analysis is similar for the other preferred examples of Peeters, in which the R_1 groups are all considerably different from applicants' R_1 groups.

Like RU 38486 the structure of the applicants' steroid compounds is not suggested by any of the preferred compounds of Peeters, et al. Thus Peeters, et al, do not establish a case of *prima facie* obviousness of any of the compounds of claim 7.

Furthermore the applicants have tested their steroid compounds of formula I against RU 38486 and have found that the steroid compounds of formula I are unexpectedly better than the closest prior art compounds of Peeters, et al, represented by RU 38486. These comparative experimental results are reported in applicants' specification on page 5 to 7 and in Table I. Reference is made to the description of the comparative experimental results on those pages.

During these comparative experiments the glucocorticoid antagonists were tested for efficacy by incubating an exemplary compound to be tested together with a glucocorticoid in a test system including glucocorticoid receptors. The reduction of the glucocorticoid-mediated action in this test system in the presence of the antagonist was measured. The glucocorticoid-mediated suppression of testoterone biosynthesis in Leydig cells is reduced or completely abolished by the glucocorticoid antagonists of the present invention.

In Table 1 in applicants' specification measurements of relative binding efficiencies of the glucocorticoid antagonists of the present invention and the prior art RU 38486 are reported. The binding efficiencies of these glucocorticoid antagonists are reported relative to a well-known glucocorticoid, dexamethasone, in the case of binding to the glucocorticoid receptor and progesterone in the case of progesterone receptor binding.

As can be seen from Table 1, the compounds of the invention or used according to the invention are significantly better dissociated, meaning that they bind satisfactorily to the glucocorticoid receptor and bind only slightly with the progesterone receptor compared to RU 38486, 11β-(4-dimethylamino)phenyl-17β-hydroxy-17α-propyn-1-yl-estra-4,9-dien-3-one, RU 38486 is a very active, but not very selective, substance. As a result if a drug includes RU 38486 it will induce significant side effects because of the binding of RU 38486 with other steroid hormone receptors, such as the progesterone receptor.

Hence, the compounds of claim 7 can potentially be used for the treatment of glucocorticoid-mediated hypogonadism, sexual dysfunction or infertility, but RU 38486 cannot be used without unacceptable side effects due to its binding with progesterone and other hormone receptors.

Thus the data in Table 1 in applicants' specification is comparative evidence of unexpectedly better properties for the steroid compounds according to the present invention in comparison to the closest prior art compound of Peeters, et al, namely RU 38486. Such evidence of unexpectedly reduced side effects and interactions for the compounds of the invention cannot be ignored

and overcomes any case of prima facie obviousness based on Peeters, et al. See M.P.E.P. 716.

With respect to the method claims 11 to 13 a method for treating glucocorticoid-mediated hypogonadism, sexual dysfunctions and/or infertility is not disclosed in any of the prior art references, Peeters, et al; Gebhard or Philbert. WO "536" (Peeters, B) describes the use of antiglucocorticoids for treatment of anxiety disorders. Gebhard describes a number of substances for the treatment of diseases mediated by certain glucocorticoids, such as Cushing's syndrome, diabetes, glaucoma, depression, arteriosclerosis, adiposity, high blood pressure, sleep disorders and osteoporosis. Philbert describes new steroids with antiglucocorticoid activity in warm-blooded animals, including humans.

Thus these prior art references do not disclose or suggest the claimed treatment method of the new claims 11 to 13 or the pharmaceutical compositions of new claims 14 to 16. Peeters, et al, does not establish a case of prima facie obviousness of claims 11 to 16.

For the foregoing reasons and because of the new features and limitations in the new claims, it is respectfully submitted that the new claims 7 to 16 should not be rejected under 35 U.S.C. 103 (a) over Peeters, et al.

B. Peeters, et al and Philbert, et al

Claims 1 to 6 were rejected under 35 U.S.C. 103 (a) over Peeters, et al, in

combination with Philbert, et al.

The preferred compounds of Peeters, et al, are not isomers of applicants' compounds of formula I. The generic formula on page 2 of Peeters, more or less, encompasses applicants' compounds or positional isomers but includes too many other compounds to establish a case of prima facie obviousness by itself.

As far as Philbert goes, Philbert leads one skilled in the art away from employing 4, 9-diene steroids in methods of therapeutic treatment. The compounds of Philbert, et al, have steroid nucleus with only a single double bond in the A ring (see claim 1, column 1, lines 35 and following of Philbert, et al).

It is well established that a reference that leads one skilled in the art away from a claimed invention should not be used under 35 U.S.C. 103 (a) to reject the claimed invention. See M.P.E.P. 2145 X. For example, the Federal Circuit Court of Appeals has said:

> "In determining whether such a suggestion [of obviousness] can fairly be gleaned from the prior art, ..It is indeed pertinent that these references teach against the present invention. Evidence that supports, rather than negates, patentability must be fairly considered." ***In re Dow Chemical Co.,*** 837 F.2nd 469,473, 5 U.S.P.Q.2d 1529, 1532 (Fed.Cir. 1988)

For the foregoing reasons it is respectfully submitted that new claims 7 to 16 should not be rejected under 35 U.S.C. 103 (a) as obvious over a combination of Peeters, et al, and Philbert, et al.

Should the Examiner require or consider it advisable that the specification, claims and/or drawing be further amended or corrected in formal respects to put this case in condition for final allowance, then it is requested that such amendments or corrections be carried out by Examiner's Amendment and the case passed to issue. Alternatively, should the Examiner feel that a personal discussion might be helpful in advancing the case to allowance, he or she is invited to telephone the undersigned at 1-631-549 4700.

In view of the foregoing, favorable allowance is respectfully solicited.

Respectfully submitted,

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